Remarks

Claims 29, 31-33, and 40-44 are pending. Claims 29 and 33 have been amended. New claims 42-44 have been added. Support for the inclusion of analogues of NRH having formula I in claim 29 can be found in the originally filed application, for example, at page 49, line 25 to page 50, line 7; and page 51, lines 7-8. Support for new claim 42 can be found, for example, at page 50, line 12 to page 51, line 1. Support for new claim 43 can be found, for example, at page 51, line 4. Support for new claim 44 can be found, for example, at page 51, lines 10-22.

The applicants have discovered that tumor cells express a different enzyme, NQO2, and can be killed by the administration of a prodrug, CB 1954, and an exogenous co-substrate for human NAD(P)H: quinone reductase 2 (NQO2), which is reduced nicotinamide riboside (NRH) or an analogue thereof. The method of the present invention is effective in converting the prodrug to a cytotoxic compound, the same cytotoxic compound as shown to be produced by the action of the rat NQO1 enzyme, which utilizes a different endogenous substrate. Table 1, on page 57 demonstrates that human NQO2 in the presence of an NRH co-substrate reduces CB 1954 six hundred times faster than human NQO1 and a hundred times faster than rat NQO1. The actual cytotoxic compound responsible for the cytotoxic effect is the same as that shown to elicit the effect in response to rat NQO1. The results in Table 3, on page 72, show that, surprisingly, analogues of NRH can be effective co-substrates for the enzyme NQO2 and together they can convert the prodrug CB1954 to its cytotoxic form.

Rejection Under 35 U.S.C. § 103

Claims 29, 31-33 and 40 were rejected under 35 U.S.C. § 103(a) as being unpatentable over *Biochem. Pharmaco.*, 44(9), pages 1739-1743, 1992, by Friedlos *et al.* ("Friedlos"), in view of *J. Biol. Chem.*, 269(20), pages 14502-14508, 1994, by Jaiswal ("Jaiswal"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Friedlos

Friedlos fails to teach treating a human patient with cancer, the expression of NQO2, that NRH or an analogue thereof is a co-substrate for NQO2 nor any analogue of nicotinamide riboside (reduced) (NRH) as presently claimed.

Jaiswal

Jaswal fails to teach that NRH or an analogue thereof is a co-substrate for NQO2 and any analogue of nicotinamide riboside (reduced) (NRH) as presently claimed.

The Examiner is respectfully reminded that claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992); *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). Therefore, in view of the failure of Jaiswal and Freidlos, singly or in combination, to teach, for example, any analogue of nicotinamide riboside (reduced) (NRH) as presently claimed, the pending claims are not obvious.

Claim Objections

Claim 33 was objected to for reciting claimed reagents in the alternative. Claim 41 was objected to for being dependent upon a rejected base claim. Applicants respectfully traverse these objections to the extent that they are applied to the claims as amended.

Allowance of claims 29, 31-33, and 40-44 is respectfully solicited.

Respectfully submitted,

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Date: March 3, 2003

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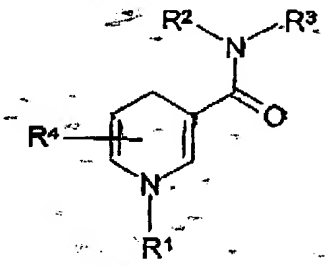
Marked Up Version of Amended Claims –

Pursuant to 37 C.F.R. § 1.121(c)(1)(ii).

29. (Twice Amended) A method of treating a human patient with a target cell to be destroyed wherein the target cell expresses NQO2 the method comprising administering to the patient a prodrug which is converted to a cytotoxic drug by the action of NQO2 and an analogue of nicotinamide riboside (reduced) (NRH) having formula I:



I

which can pass reducing equivalents to NQO2, wherein the prodrug is CB 1954, and wherein R^1 is selected from the group consisting of: substituted alkyl, including substitution by CONH2, OH, halogen, CN and COOH; alkyl; aryl; substituted aryl; $CONR^aR^b$, where R^a and R^b are independently H, alkyl, or substituted alkyl, and R^2 and R^3 are independently H, alkyl, or substituted alkyl and R^4 is any of H, alkyl, substituted alkyl, halogen, CN, COOH, $CONH_2$ or OH.

31. (Amended) The method of claim 29 wherein the analogue of NRH is able to permeate the target cell membrane.

32. (Amended) The method of claim 29 wherein the target cell is a tumour.

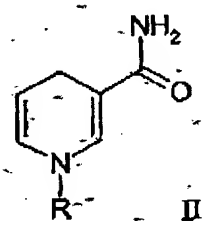
MARKED UP VERSION OF AMENDMENTS PURSUANT TO 37 C.F.R. § 1.121

33. (Twice Amended) The method of claim 29, the method further comprising determining, before administering the prodrug an analogue of NRH, whether the target cell to be treated expresses NQO2.

40. The method of claim 29 wherein the patient has cancer.

41. The method of claim 29, wherein the analogue of NRH is 1-(carboxamidomethyl)-dihydronicotinamide.

42. (New) The method of claim 29, wherein the analogue of NRH has formula II:



II

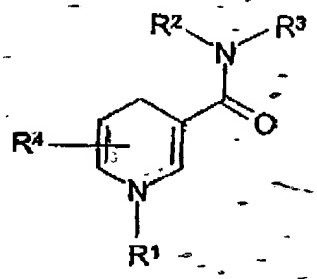
wherein R is selected from the group consisting of: substituted alkyl, including substitution by $CONH_2$, OH, halogen, CN and COOH; and alkyl.

43. (New) The method of claim 29 wherein the alkyl group is C_1 to C_6 alkyl.

44. (New) The method of claim 42 wherein R is selected form the group consisting of: $-CH_2CONH_2$; $-CH_2CH_2CH_2SO_3$; $-CH_2CH_2CH_3$; $-CH(CH_3)_2$; $-CH_2CH_2CH_2OH$; $-CH_2CH_2OH$; CH_2CH_2COOH; $-CH_2C_6H_5$; $-CH_3$; $-CH_2CH_3$; $-CH_2CH_2C_6H_5$.

Clean Version of Amended Claims Pursuant to 37 C.F.R. § 1.121(c)(1)(ii)

29. (Twice Amended) A method of treating a human patient with a target cell to be destroyed wherein the target cell expresses NQO2 the method comprising administering to the patient a prodrug which is converted to a cytotoxic drug by the action of NQO2 and an analogue of nicotinamide riboside (reduced) (NRH) having formula I:



I

which can pass reducing equivalents to NQO2, wherein the prodrug is CB 1954, and wherein R^1 is selected from the group consisting of: substituted alkyl, including substitution by CONH2, OH, halogen, CN and COOH; alkyl; aryl; substituted aryl; $CONR^aR^b$, where R^a and R^b are independently H, alkyl, or substituted alkyl, and R^2 and R^3 are independently H, alkyl, or substituted alkyl and R^4 is any of H, alkyl, substituted alkyl, halogen, CN, COOH, $CONH_2$ or OH.

31. (Amended) The method of claim 29 wherein the analogue of NRH is able to permeate the target cell membrane.

32. (Amended) The method of claim 29 wherein the target cell is a tumour.

33. (Twice-Amended) The method of claim 29, the method further comprising determining, before administering the prodrug an analogue of NRH, whether the target cell to be treated expresses NQO2.

40. The method of claim 29 wherein the patient has cancer.

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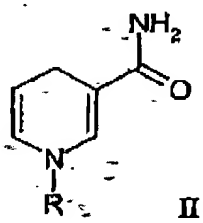
42. (New) The method of claim 29, wherein the analogue of NRH has formula II:



II

wherein R is selected from the group consisting of: substituted alkyl, including substitution by $CONH_2$, OH, halogen, CN and COOH; and alkyl.

43. (New) The method of claim 29 wherein the alkyl group is C_1 to C_6 alkyl.

44. (New) The method of claim 42 wherein R is selected form the group consisting of: $-CH_2CONH_2$; $-CH_2CH_2CH_2SO_3$; $-CH_2CH_2CH_3$; $-CH(CH_3)_2$; $-CH_2CH_2CH_2OH$; $-CH_2CH_2OH$; CH_2CH_2COOH; $-CH_2C_6H_5$; $-CH_3$; $-CH_2CH_3$; $-CH_2CH_2C_6H_5$.